FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 3568.070

U S APPLICATION NO. (If known, see 37 CFR 1 5): 09/936065

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP 00/08678	6 SEPT. 2000	14 SEPT. 1999

TITLE OF INVENTION: ADSORPTIVE MEMBRANE DEVICE FOR TREATING PARTICLE-LADEN LIQUID...

APPLICANT(S) FOR DO/EO/US: Demmer et al (Inventors)/SARTORIUS AG (Assignee)

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [X] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is attached hereto (required only if not communicated by the International Bureau).
   b. [ ] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [X] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [ ] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [X] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information:
    FORMAL DRAWINGS (4 Sheets)
    POWER OF ATTORNEY
    CERTIFICATE OF MAILING BY EXPRESS MAIL NO. EL915421548US

U.S. APPLICATION NO (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/936065		

21. ☒ The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	17 - 20 =	0	x $18.00	$ 0	
Independent claims	1 - 3 =	0	x $80.00	$ 0	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)	N/A		+ $270.00	$ 0	
TOTAL OF ABOVE CALCULATIONS =				$	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$	
SUBTOTAL =				$	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$ N/A	
TOTAL NATIONAL FEE =				$ 860	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 40	
TOTAL FEES ENCLOSED =				$ 900	
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $ 900 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 03-1550. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO.

Dennis E. Stenzel

SIGNATURE

DENNIS E. STENZEL

NAME

REG. NO. 28,763

REGISTRATION NUMBER

CERTIFICATE OF MAILING BY

"EXPRESS MAIL"

Express Mail No. EL915421548US

Date of Deposit: September 5, 2001

I hereby certify that the patent application attached hereto entitled **ADSORPTIVE MEMBRANE DEVICE FOR TREATING PARTICLE-LADEN LIQUID FEEDS**, Wolfgang Demmer and Dietmar Nussbaumer, inventors, is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service on the date indicated above and is addressed to BOX PATENT APPLICATION, ATTN: DO/EO/US, Commissioner for Patents, Washington, D.C. 20231.

Dwight Bergquist-Moody

PCT/EP00/08678
WO 01/19483 A1

DEVICE THROUGH WHICH PARTICLES CAN PASS, FOR SEPARATING SUBSTANCES USING POROUS, FLAT, ADSORPTION MEMBRANES

Description

German text: Page 1

The invention concerns a particle passing apparatus for the carrying out of material separation by means of the permeation of liquids through more than one layer of porous, flat adsorption membranes.

By the term, "porous, flat adsorption membranes", (i.e. a membrane adsorber) microporous, flat membranes are to be understood , which possess on their surface functional groups and/or ligands or reactants, which have the capability for exchange action with at least one substance of a liquid phase which is in contact with said membrane (WO-A1-92-00805, Sartorius, AG). The transport of the liquid phase through the adsorption membranes is convective. The designation "adsorption membranes" is a general term for various kinds of adsorption membranes such as ion exchange membranes, ligand membranes, affinity membranes and activated membranes. These so designated membranes themselves are subdivided in accord with their functional groups, ligands and reactants into various adsorption membrane types.

The apparatuses in accord with the invention can be installed for the treatment of particle bearing liquids, as these occur, for example, in biological technology, in chemical and food industries, or in water treatment or in wastewater handling.

In this way, for example, biologically active substances are produced by cell cultures. For the obtaining of the said active substances, the cells must be, as a rule, removed and separated by means of centrifuging and/or filtration, so that, from the remaining liquid, the desired material can be isolated.

German text: Page 2

For the avoidance of this additional step in particle separation, K. H. Kroner et al. describes a procedure for crossflow filtration with adsorption-affinity membranes for the primary separation of proteins in an example of the isolation of the enzyme malate dehydrogenase from E-coli and baker's yeast with the aid of a Cibacron blue modified membrane (Bioforum 12, 455-458 (1992)). In the execution of the process, the particle loaded fluid flow was caused to proceed directly to the cell remnant run-off by tangential flow over one membrane layer. The targeted substance found in the filtrate collected in the said membrane. After the removal of the particles by washing the membranes, the targeted substance was recovered by suitable solvents. A disadvantage of this procedure, lies in the non-uniform permeation of the target substance through the one membrane layer. This disadvantage can be overcome by a cross-flow filtration apparatus as shown in Fig. 12 of DE-PS 197 11 083. However, this still possesses a disadvantage, in that it must be driven by a high energy input, so that, first, a higher permeate flow is assured and second, a sufficient overflow velocity for the entrainment of the particles with the fluid flow is achieved. Otherwise, the first membrane would be blocked and the entire permeation process defeated. In comparison, the dead-end filtration units disclosed by DE-PS 197 11 083 and DE-OS 44 32 628, exhibit, because of the use of a plurality of layers of porous, adsorption membranes, a uniform throughput of the targeted substance at a high adsorption capacity. However, in this case, the liquid feed must, in any case, be particle free, in order to prevent a blockage of the filtration units.

Thus, the invention has the purpose, of creating an apparatus for the carrying out of material separation by means of a permeation of particle carrying liquids through porous adsorption membranes, which characterizes itself by a high adsorption capacity, a uniform throughput of the target material and a simple construction.

This purpose is achieved by the object of Claim 1

German text: Page 3

Surprisingly, it was discovered, that substance separation by means of adsorption membranes, even with liquids bearing a heavy load of particles, could be realized, if the equipment has more than one layer of porous, flat adsorption membranes. Such membranes are to be distanced, one from the other and possess at least one opening or preferably, a plurality of openings, for the passage of particles. In operation, the first layer of porous membrane, which has at least one opening, is subjected to a flow, under pressure, of a particle laden liquid from which a material therein dissolved is to be separated. A first portion of the liquid permeates particle-free through the pores of the first layer of the membrane, whereby the target material is adsorbed in the interior of the said membrane. The remaining portion of the liquid, together with the particles, flows through the at least one hole of the first layer into that space which is created between the first and the next spatially separated layer, wherein it joins the permeate which simultaneously has penetrated the membrane. The so united portions of the liquid can now flow over the surface of the second layer of the flat, adsorptive membrane, until the portion carrying particles flows through the at least one hole of this second membrane. Again, in the same manner as above, a portion of the liquid permeates particle free through pores of this second membrane. Both portions of the liquid now collect together in the space created by the separation of the second and the next layers. This described process repeats itself so often, until that liquid of the joined liquids of the particulate laden portion and the permeate exit from the final layer of the flat, adsorption membrane through the at least one hole therein. At this point, the liquid exiting from the particle passing device is completely, or nearly, totally freed of the target material.

In the case of a plurality of holes, these are arrayed in a regular or irregular arrangement in the membranes of the equipment. These holes have such an opening size, that passage therethrough by the particles in the liquids is possible. The diameter of the said holes runs as a multiple of the nominal pore diameter of the employed microporous adsorption membranes. The holes should be, however, smaller than 100-times the diameter of the largest particle in the liquids. For an optimal employment of the entire

membrane volume for adsorption, it has shown itself as advantageous if the said holes in neighboring

German text: Page 4

layers are offset one from the other. This is true even when the number of the holes in a membrane unit is not large and/or they are of small diameter. The least fraction that a hole can take, relative to the area of a layer of the membrane, would run from 20 % down to 4 %. The holes can be made be optionally in shape, advantageously, they can be in the shape of a slot or a circle with a diameter of 0.01 to 20 mm, preferably, 0.5 to 2 mm. The neighboring layers of the porous flat adsorption membranes, by means of spacer elements, are arranged parallel to one another with a gap between them in a range of 0.1 to 5 mm, preferably between 0.2 to 1 mm. For spacers, consideration can be given to webs, gratings, webbing, knitted material or matting, which characterize themselves by a favorable ability to pass particles.

The flat adsorption membranes should have a pore diameter in a range between 0.1 to 10 μm, with preference given to 3 to 5 μm. Adsorption membranes with smaller pore diameters exhibit too restricted a permeability for practical usage, whereas in the case of adsorption membranes with large pores, the danger of blockages by the impingement of smaller particles exists. Flat membranes are employed as adsorption membranes, which carry functional groups and/or ligands or reactants, which have the capability for an exchange activity which removes from the liquid at least one material, preferably the targeted material.

The apparatus can be constructed as a flat module or, in an advantageous embodiment of the invention, also as a wound module. Particularly advantageous is a modular cylindrical embodiment, as this is described in DE-PS 197-11-083.

The invention shall now be more closely examined and described with the aid of the drawings 1 to 4. There is shown in:

Fig. 1 schematically, a section through one embodiment of the invented device,

German text: Page 5

Fig. 2 one version of an arrangement of holes in a layer of a flat adsorption membrane,

Fig. 3 a curve of a typical material separation and

Fig. 4 an exploded presentation of another embodiment of the arrangement of the holes in adjacent layers of the flat adsorption membrane.

In accord with Fig. 1, the particle passing device 1 comprises a housing 2 with a liquid inlet 3 and a liquid outlet 4. In the housing 2 are to be found more than one layer of porous adsorption membranes 5, arranged in such a manner, that during operation of the device, 1, the liquids from the inlet 3 to the liquid outlet 4 must sequentially pass the said layers. The layers of the adsorption membrane 5 are provided with holes 6 for the passage of the particles 8 borne in the feed liquid 7. For the sake of clarity, only few holes 6 are shown. The layers of the adsorption membranes 5 are sealingly covered in their peripheral rim areas next to the housing 2 by means of a sealant 9. The layers of the adsorption membrane 5 are distanced, one from the other, for the creation of a space 10 for the collection of a first portion 11 of the liquid 7 which has permeated through the adsorption membrane, and also so distanced for the remaining second portion of the particle laden liquid which has passed through the holes 6 of the layers 5. The offset distance of the layers of the adsorption membrane 5 is stabilized by means of spacers 13, which may be in the form of particle passing gratings, mesh, knitted material or matting placed between the layers 5. For better flowing conditions, the first layer 5 and for a better collection of the fluid 7 after the last layer of the adsorption membrane 5, appropriate flow guidance apparatuses, namely in the form of the said spacers 13 are furnished.

The explosion type presentation of Fig. 4 shows an additional embodiment of the arrangement of the holes 6 in the sequentially spaced layers of the flat adsorption membranes 5 as well as the thereto attendant spacers 13. These elements are, for instance, installed in a (not shown) housing with liquid inlet/outlet fittings and again sealed at the edges.

German text: Page 6

Example 1

Two meters of a 6 cm wide, strongly basic adsorption membrane of the type SARTOBIND® Q (Sartorius, AG) were provided with holes in an arrangement such as presented in Fig. 2. The holes were spaced from each other at a distance of 1.8 cm and were of diameter 3.5 mm. The holes took up an area of 1.8 % of the area of the frontal membrane surface. This membrane strip was worked up together with a 6 cm wide mesh band of propylene to make a cylinder module in accord with DE-PS 197 11 083.

The cylinder module received, by means of a tube-pump, one liter, at a pH value of 8.3, of a particle laden liquid (the feed solution) of a commercially available bovine serum albumin (BSA) – of the firm of Kräber, Hamburg – and air dried bakers yeast in a buffer of the composition of 0.01 M tris (hydroyl-methyl) amino methane (TRIS), along with concentrated hydrochloric acid. The feed rate was 0.6 l/min. The liquid leaving the cylinder module was conducted through a flow photometer of the firm of Wedgewood, San Carlos, USA. The absorption of the solution was determined to be 280 nm and was continually recorded. After the passage of the liter of liquid, the device was washed with the buffer until the absorption of 280 nm was reduced to read 0 nm. Subsequently, first the BSA was eluted from the cylinder module with a solution of 0.25 M sodium chloride in the buffer and finally the bound yeast removed by 1M sodium chloride in the buffer. During the entire procedure, no significant increase of the pressure occurred. Thereafter, the cylinder module stood available for an addition cycle. The example was repeated.

Fig. 3 shows the typical curve of such an experiment. An immediate break through of the yeast particles occurred through the cylinder module, as is represented by the steep climb at the start of the curve.

After the washing out of all UV-absorbing particles, the BSA was eluted with 0.25 M NaCl in the buffer (first large peak in the curve), and then the yeast, still retained in the cylinder module was desorbed by with 1 M NaCl in the buffer to give the second peaking. The dynamic binding capacity (reaching of 10 % of the concentration of the

German text: Page 7a

added BSA solution in the run-off) proved to be 0.38 mg/cm^2 membrane surface. The static binding capacity was 0.5 mg/cm^2 membrane surface. The following results were achieved:

First Run:

Fraction	Volume [l]	Absorption [E 280 nm]	Turbidity	BSA [g]	Recovery of BSA [%]
Feed sol.	1	0.6	+	1	-----
0.25 M NaCl	0.58	0.8	-	0.8	80
1 M NaCl	0.5	not meas	+	not meas	----

Second Run

Fraction	Volume [l]	Absorption [E 280 nm]	Turbidity	BSA [g]	Recovery of BSA [%]
Feed sol.	1	0.6	+	1	----
0.25 M NaCl	0.58	0.66	-	0	6
1 M NaCl	0.5	not meas	+	not meas	----

Example 2

In an additional example 10 g air dried commercially obtainable baker's yeast was suspended in one liter of the buffer described in Example 1 and this suspension was conducted in a circulation in the cylinder module as indicated in Example 1. The average entry pressure was 0.1 bar and did not change itself significantly during the 30 minute time to run the example. Thereafter to the suspension, 1 g BSA was added and this mixture run through the cylinder module.

After freely washing, as described above in the Example 1, the BSA was eluted with 0.25 M NaCl in the buffer.

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At this point, 0.41 g BSA were recovered. Therewith, the dynamic binding capacity was reduced by 48 %.

The cylinder module was then washed with 1 M NaCl in the buffer, and then treated with 1 M NaOH and allowed to stand for 10 minutes. Subsequently a wash was carried out with 1 M NaOH and thereafter again with 1 M NaCl and finally washed with only the buffer.

The cylinder module was again charged with BSA. The following results were achieved:

Third run

Fraction	Volume [l]	Absorption [E 280 nm]	Turbidity	BSA [g]	Recovery of BSA [%]
Feed sol.	1	0.6	+	1	---
0.25 M NaCl	0.5	1.06	-	0.86	86
1 M NaCl	0.5	not meas	+	not meas	---

The static binding capacity ran still 90 % of the value of that of the first run of Example 1.

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CLAIMS

Claimed is:

1. A particle passing device (1) for the carrying out of material separation by means of permeation of liquids through more than one slayer of porous, flat, adsorption membranes (5), which are spaced apart from one another and are provided with at least one hole (6) for he passage of the particles (8), whereby the device (1), possesses a liquid inlet (3) proximal to the first layer, and also a liquid outlet (4) proximal to the last layer, and the separated layers of the flat membranes (5), in their peripheral edge zones are made impermeable for the liquids in such a way, that the liquids to be treated (7) from the liquid inlet (3) to the liquid outlet (4) must pass through the layers (5), sequentially, whereby in each layer (5), respectively, a first portion (11) of the liquid to be treated permeates free of particles through the pores of the flat adsorption membrane and the remaining portion (12) of the liquid to be treated (7), laden with the particles, passes through the at least one hole (6) in the membrane (5) and both partial flows (11, 12) are once again united on the subsequent membrane.

2. A device (1) in accord with Claim 1 in which the at least one hole (6) of the neighboring layers (5) are offset from one another.

3. A device (1) in accord with in accord with Claim 1 or Claim 2, in which the at least one hole (6) occupies a portion relative to the area of the layer of the flat membrane (5) of up to 20 %, advantageously, up to 4 %.

4. A device (1) in accord with one of the foregoing Claims, in which the at least one hole (6) is construction in circular shape and possesses a diameter of 0.01 to 20 nm, preferably 0.5 to 2 mm.

5. A device (1) in accord with one of the foregoing claims, in which the neighboring layers of the porous, flat membrane (5), by means of a spacer (13),maintain, in parallel arrangement, a separating space of 0.1 to 5 mm, preferably between 0.2 to 1 mm, one from the other.

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6. A device (1) in accord with Claim 5, in which the spacer 13 is comprised of webs, grating, mesh or matting.

7. A device (1) in accord with Claim 1, in which the flat membrane (5) possesses a pore diameter in a range between 0.1 and 10 µm, preferably between 3 to 5 µm.

8. A device (1) in accord with Claim 1, in which the flat membranes (5) carry functional groups, and/or ligands, or reactants, which have the capability of joining in exchange action with at least one material in the liquid 7.

9. A device (1) in accord with one of the foregoing Claims, in which the layers (5) are shaped into a winding and the device (1) is designed as a wound module.

* * *

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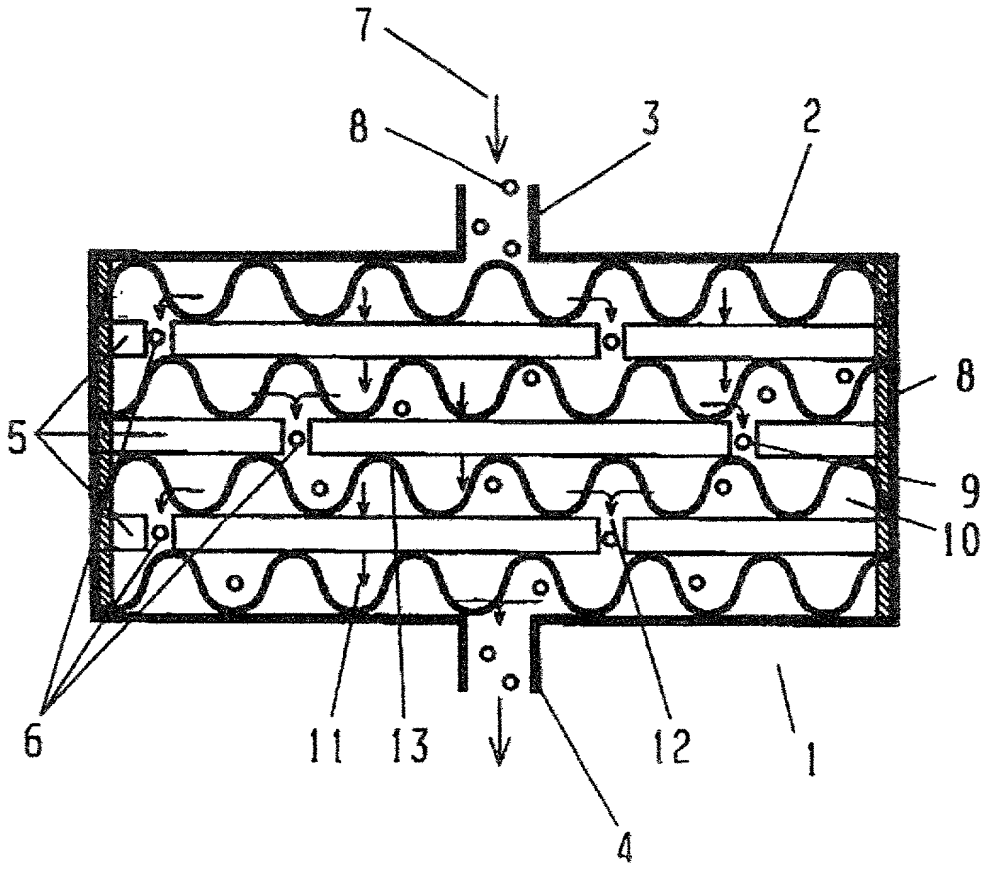

Fig. 1

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WO 01/19483 PCT/EP00/08678

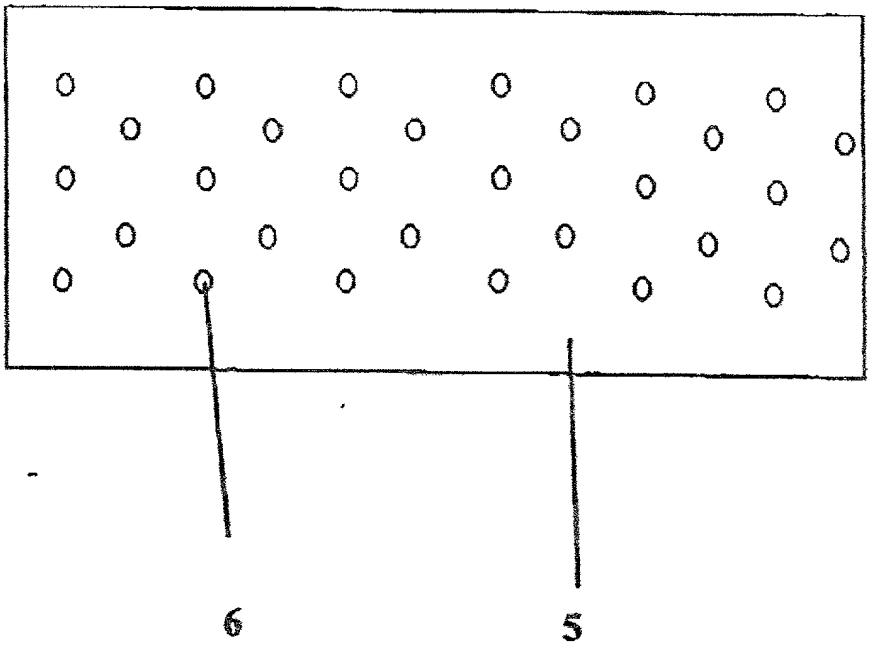

Fig. 2

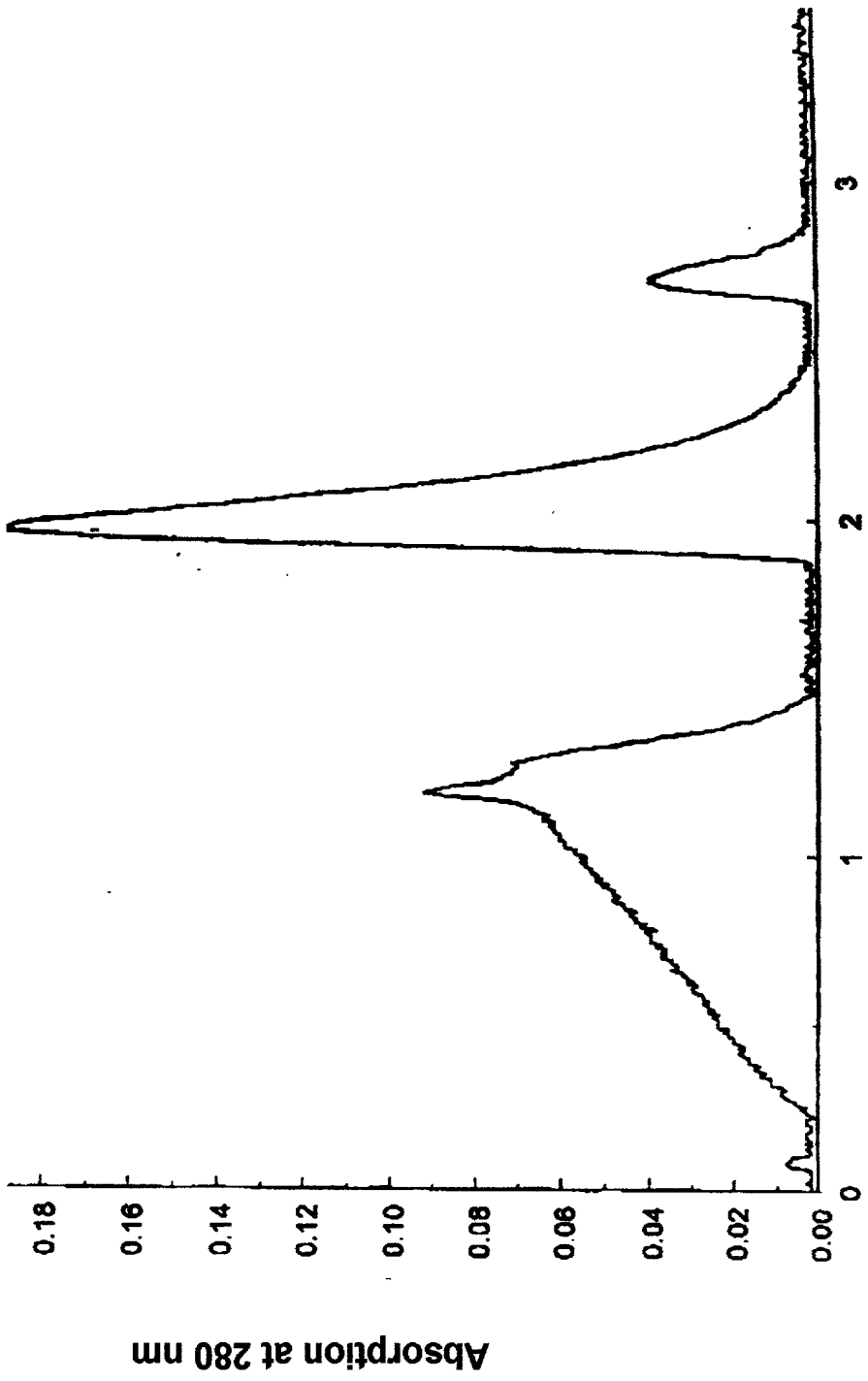
Absorption at 280 nm
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
1
2
3
Quantity of liquid in liters

Fig. 3

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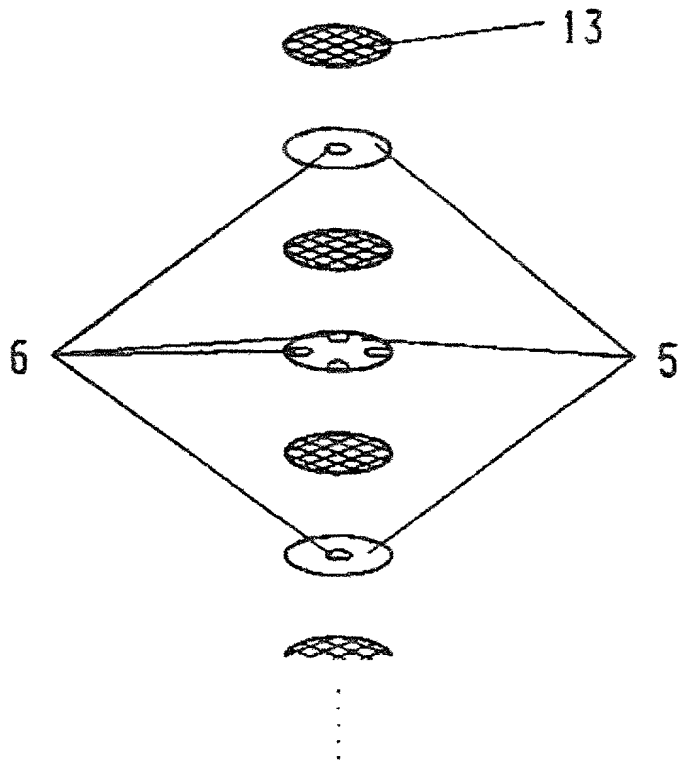

Fig. 4

ADSORPTIVE MEMBRANE DEVICE FOR TREATING PARTICLE-LADEN LIQUID FEEDS

Pursuant to 35 USC §365(b) and 120, the priority of PCT/EP 00/08678 filed 6 September 2000 and DE 199 43 921.4 filed 14 September 1999 is claimed.

BACKGROUND OF THE INVENTION

Membrane adsorbers comprising microporous, flat membranes having chemical moieties capable of binding target substances on their surfaces such as functional groups, ligands, ion-binding sites or other reactants are well known, as is their use for separation of such target substances from liquid feeds. See WO 92 00805 A1. The liquid feed is transported through the membrane adsorber by convective transport.

Typically, membrane adsorbers are used as part of a two-step process of (1) separation of particles by centrifugation or by cross flow filtration and (2) separation of the desired bioactive substance by the membrane adsorber. In an attempt to combine the step of particle separation with separation of the target substance in a single pass through the membrane adsorber, a crossflow filtration process has been suggested using Cibacron blue-modified membrane for the isolation of the enzyme maleate dehydrogenase from E-coli and baker's yeast. 12 *Bioforum* 455 (1992). According to this process, the particle-laden fluid feed is ridden of cell remnants by directing the feed tangentially across one membrane layer, allowing cell fragments to remain on the membrane's surface while the target substance is collected in the membrane. After removal of the cell fragments by washing the membranes, the target substance is eluted with appropriate solvents. A disadvantage of this process lies in the non-uniform permeation of the target substance through the single membrane layer. This disadvantage can be overcome by the utilization of a

spiral-wound cross-flow filtration apparatus as shown in Fig. 10 of U.S. Application Serial No. 09/397,456 filed September 16, 1999 now U.S. Patent No. _____ , the pertinent disclosure of which is incorporated herein by reference. However, the process still has an additional drawback in that it requires a large driving force to provide a higher permeate flow and a sufficient overflow velocity for entrainment of the particles with the fluid feed. Otherwise, the first membrane layer would be blinded and the entire permeation process defeated.

Accordingly a primary object of the invention is the provision of a simultaneous separation of particles and target substances from liquid feeds through porous adsorption membranes , characterized by a high adsorption capacity, a substantially uniform flux and by simple construction.

BRIEF SUMMARY OF THE INVENTION

Rather surprisingly, it has been found that separation by adsorption membranes, even with liquids bearing a heavy load of particles, can take place with the use of more than one layer of porous, flat adsorption membranes so long as they are spaced apart from each other and provided with at least one, but preferably a plurality, of apertures for the passage of particles. In operation, the first such membrane layer is subjected to a pressurized liquid particle-laden fluid feed containing one or more target substances. A first portion of the feed permeates particle-free through the pores of the first layer of the membrane, whereby a portion of the target substance is adsorbed in the interior of that first membrane layer. The remaining particle-bearing portion of the feed flows through the aperture(s) of the first membrane layer into a space between the first and the second membrane layer, wherein it joins the permeate which simultaneously has penetrated the first membrane layer. The so-united portions of the feed then flow over

the surface of a second membrane layer with the particle-laden portion again flowing through the aperture(s) of this second membrane layer and the particle-free portion permeating through pores of the second membrane layer. The particle-laden and particle-free portions again collect together in a space between the second and third layers, and so on, with each pass passing particles in the feed and at the same time capturing the target substance by adsorption in the membrane layers, resulting in a final permeate that is entirely or nearly entirely free of the target substance, with the particles passing through the device and being discarded. The target substance is then eluted with one or more appropriate eluting agents.

The device of the present invention can be used for separations involve particle-bearing liquids, in the fields of biotechnology, in the chemical and food industries, in water treatment or in wastewater handling. A specific example of the utility of the invention would be in the recovery of biologically active substances produced by cell cultures coupled with the removal and separation of cells and cell fragments.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Fig. 1 is a cross-sectional schematic of an exemplary embodiment of the present invention.

Fig. 2 is a plan view of an adsorption membrane of the present invention showing exemplary particle-passing apertures therein.

Fig. 3 is an exploded perspective view of another exemplary arrangement of particle-passing apertures, spacers and adsorption membranes in the separation device of the present invention.

Fig. 4 is a graph of a typical material separation conducted by the separation device of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Referring to the drawings, wherein the same numerals refer to like elements, there is shown in Fig. 1 a separation device 1 comprising a housing 2 with a feed inlet 3 and a discharge or permeate outlet 4. Inside housing 2 are multiple layers of porous adsorption membranes 5 arranged so that liquid filtration feed 7 must sequentially pass through the membrane layers. Each layer of adsorption membranes 5 is provided with particle-passing apertures 6 for the passage of particles 8 borne in the liquid filtration feed liquid 7. For the sake of illustration, only a few apertures 6 are shown in Fig. 1; Fig. 2 shows an exemplary arrangement of a multiplicity of such apertures. The layers of adsorption membranes 5 are sealed fluid-tight at their peripheries near the ends of housing 2 by a sealant 9. The layers of adsorption membranes 5 are separated from each other so as to form particle-free permeate plenum 10 for the collection of particle-free permeate 11 of filtration feed 7 which has permeated through adsorption membranes 5, and also so as to permit the remaining particle-laden permeate to pass through apertures 6. The separation of the layers of adsorption membrane 5 is supported by spacers 13, which may be in the form of a particle-passing web, mesh, woven material or matting. For better flux, spacers 13 are preferably included between the walls of housing 3 and both the first and the last layer of adsorption membranes 5.

The exploded perspective view of Fig. 3 shows an additional exemplary embodiment of the arrangement of apertures 6 and spacers 13 in the sequentially spaced layers of the flat adsorption membranes 5. These elements may be installed in a housing (not shown) having liquid inlet/outlet fittings and again sealed fluid-tight at their peripheries.

In the case of a plurality of apertures, the same may be arranged in a regular or irregular pattern in

the membrane layers, and are sized so as to permit passage of particles in the feed. The diameter of the apertures runs as a multiple of the nominal pore diameter of the microporous adsorption membranes used in the device, with an upper limit of smaller than 100 x the diameter of the largest particles in the feed. To maximize the volume of membrane available for adsorption, it is best if the apertures in neighboring layers are offset from each other. This is true even when the number of apertures in the membrane separation device is not large and/or they are small in diameter. Such apertures preferably take up from 1 to 20% of the surface area of a layer of the membrane, preferably from about 2 to about 4%. The apertures may be in virtually any shape, but are preferably in the shape of a slot or a circle, the latter shape having a diameter of from about 0.01 to about 20 mm, preferably from about 0.5 to about 2 mm. The neighboring layers of the porous flat adsorption membranes 5 are preferably separated by spacers 13 arranged parallel to one another with a gap between them in the range of from about 0.1 to about 5 mm, preferably from about 0.2 to about 1 mm. Spacers 13 may be formed from webs, woven material or matting, so long as the material permits passage of particles.

The flat porous adsorption membranes 5 preferably have a pore diameter in a range from about 0.1 to about 10 μm, more preferably from about 3 to about 5 μm. While adsorption membranes with smaller pore diameters are insufficiently permeable for use in the present invention, even in the case of membranes having the aforesaid pore size range, there is the potential for blockage by the impingement and build-up of smaller particles. Membranes 5 carry functional groups and/or ligands or reactants, which have the capability of binding target substances from the feed.

The apparatus can be constructed as a flat module or, in an advantageous embodiment of the

invention, as a spiral wound module. A particularly preferred design is the type of cylindrical spiral wound module disclosed in U.S. Application Serial No. 09/397,456 filed September 16, 1999, now U.S. Patent No. _____, incorporated herein by reference.

Example 1

Two meters of a 6 cm wide, strongly basic ion exchanger adsorption membrane (SARTOBIND® Q, Sartorius AG of Goettingen, Germany), were provided with 3.5 mm diameter apertures in substantially the arrangement shown in Fig. 2, spaced apart from each other 1.8 cm and taking up 1.8% of the surface area of the membrane. This membrane strip was spirally wound together with a 6 cm wide band of polypropylene mesh to make a cylindrical module of the design shown in U.S. Application Serial No. 09/397,456 filed September 16, 1999, now U.S. Patent No. _____. For a First Run one liter of a particle-laden bovine serum albumin (BSA) feed solution (pH 8.3) containing particles of air-dried bakers yeast in a TRIS buffer solution (0.01 M tris (hydroxymethyl) amino methane) adjusted to pH 8.3 with concentrated HCl, was fed to the module at a rate of 0.6 L/ min. Permeate from the module was conducted through a flow UV photometer which continuously recorded UV absorption at 280 nm, representing the absorption of yeast particles and cell debris. After passage of the entire liter of liquid feed the module was flushed with the TRIS buffer until the absorption at 280 nm was nil. Subsequently, first the BSA was eluted form the module with a solution of 0.25 M NaCl in the TRIS buffer and finally the non-specifically bound yeast particles were eluted with a solution of 1M NaCl in the TRIS buffer. During the entire procedure, no significant increase of pressure in the module occurred.

Thereafter, the module was ready for an additional cycle, and the cycle was repeated (Second Run). Fig. 4 is a plot of the data from the foregoing

separation, which shows an immediate breakthrough of the yeast particles, as represented by the steep incline A at the start of the curve. The TRIS buffer flush was begun at point B in FIG. 4 and resulted in the elution of all UV-absorbing particles. The BSA was then eluted with 0.25 M NaCl in the TRIS buffer (peak C in the curve), and then the yeast still retained in the module was desorbed by 1 M NaCl in the TRIS buffer to give the second peak D. The dynamic binding capacity (reaching of 10% of the concentration of the added BSA solution in the run-off) was 0.38 mg/cm^2 of membrane surface area. The static binding capacity was 0.5 mg/cm^2 of membrane surface area.

Example 2

Ten grams air-dried baker's yeast were suspended in one liter of the TRIS buffer of Example 1 and this suspension was circulated in the module of Example 1 in the same manner as in Example 1 for a Second Run. The average feed pressure was 0.1 bar and did not change significantly during the 30 minutes taken to run the sample. Thereafter, 1 g BSA was added to the suspension and this mixture was run through the module. After the flushing with the TRIS buffer as described in Example 1, the BSA was eluted with a solution of 0.25 M NaCl in the TRIS buffer. At this point, 0.41 g BSA was recovered, showing a 48% reduction in static binding capacity due to yeast particles occupying binding sites on the adsorption membrane.

The results from the First and Second Runs are summarized in the tables below.

First Run

Fraction	Volume (L)	Absorption (280 nm)	Turbidity	BSA (g)	Recovery of BSA (%)
Feed sol.	1	0.6	+	1	-----
0.25 M NaCl	0.58	0.8	-	0.80	80
1 M NaCl	0.5	NM	+	NM	-----

Second Run

Fraction	Volume (L)	Absorption (280 nm)	Turbidity	BSA (g)	Recovery of BSA (%)
Feed sol.	1	0.6	+	1	----
0.25 M NaCl	0.58	0.66	-	0.64	64
1 M NaCl	0.5	NM	+	NM	----

NM = not measured

Example 3

For a Third Run, the module of Example 2 was then flushed with a 1 M NaCl solution in the TRIS buffer and then with a 1 M NaOH solution and allowed to stand for 10 minutes so as to remove the bound yeast particles and so regenerate the binding capacity of the adsorption membrane. Subsequently the module was again flushed with 1 M NaOH followed by flushes with solutions of 1M NaCl and with the TRIS buffer. The module was again charged with BSA. The static binding capacity stayed at 90% of the 0.5 mg/cm^3 value recorded for the First Run of Example 1. The results from the Third Run are summarized in the table below.

Third Run

Fraction	Volume (L)	Absorption (280 nm)	Turbidity	BSA (g)	Recovery of BSA (%)
Feed sol.	1	0.6	+	1	----
0.25 M NaCl	0.5	1.06	-	0.86	86
1 M NaCl	0.5	NM	+	NM	----

NM = not measured

The terms and expressions which have been employed in the foregoing specification are used therein as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding equivalents of the features shown and described or portions thereof, it being recognized that the scope of the invention is defined and limited only by the claims which follow.

What is claimed is:

1. A device for the separation of particles and at least one target substance from a particle-laden liquid feed comprising:

(a) a housing having a liquid feed inlet and a permeate outlet; and

(b) at least two adjacent porous adsorption membrane layers sealed fluid-tight in their peripheries and spaced apart from each other and having at least one aperture in each layer, with each aperture sized so as to permit the passage of particles present in a liquid feed containing at least one target substance.

2. The device of claim 1 wherein said membrane layers carry at least one group capable of binding at least one of said at least one target substance and selected from the group consisting of a functional group, a ligand and an ion exchange site.

3. The device of claim 1 including at least one spacer between said at least two adjacent membrane layers.

4. The device of claim 3 wherein said adjacent membrane layers are substantially parallel to each other.

5. The device of claim 4 wherein said adjacent membrane layers are separated from each other by a distance of from about 0.1 to 5 mm.

6. The device of claim 5 wherein said distance is from about 0.2 to about 1.0 mm.

7. The device of claim 3 wherein said at least one spacer comprises a material selected from the group

consisting of a web, a mesh, a woven material and matting.

8. The device of claim 1 wherein said at least one aperture in said at least two adjacent membrane layers are offset from each other.

9. The device of claim 1 wherein said at least one aperture takes up an area of up to about 20% of the surface area of said at least two membrane layers.

10. The device of claim 9 wherein said area is from about 2 to about 4%.

11. The device of claim 1 wherein the shape of said at least one aperture is selected from a slot and a circle.

12. The device of claim 11 wherein said at least one aperture is in the shape of a circle and its diameter is from about 0.01 to about 20 mm.

13. The device of claim 12 wherein said diameter is from about 0.5 to about 2 mm.

14. The device of claim 1 wherein said membrane layers are spiral wound.

15. The device of claim 14 wherein said membrane layers are enclosed within a module.

16. The device of claim 1 wherein said membrane layers have a pore diameter ranging from about 0.1 to about 10 μm.

17. The device of claim 16 wherein said pore diameter is from about 3 to about 5 μm.

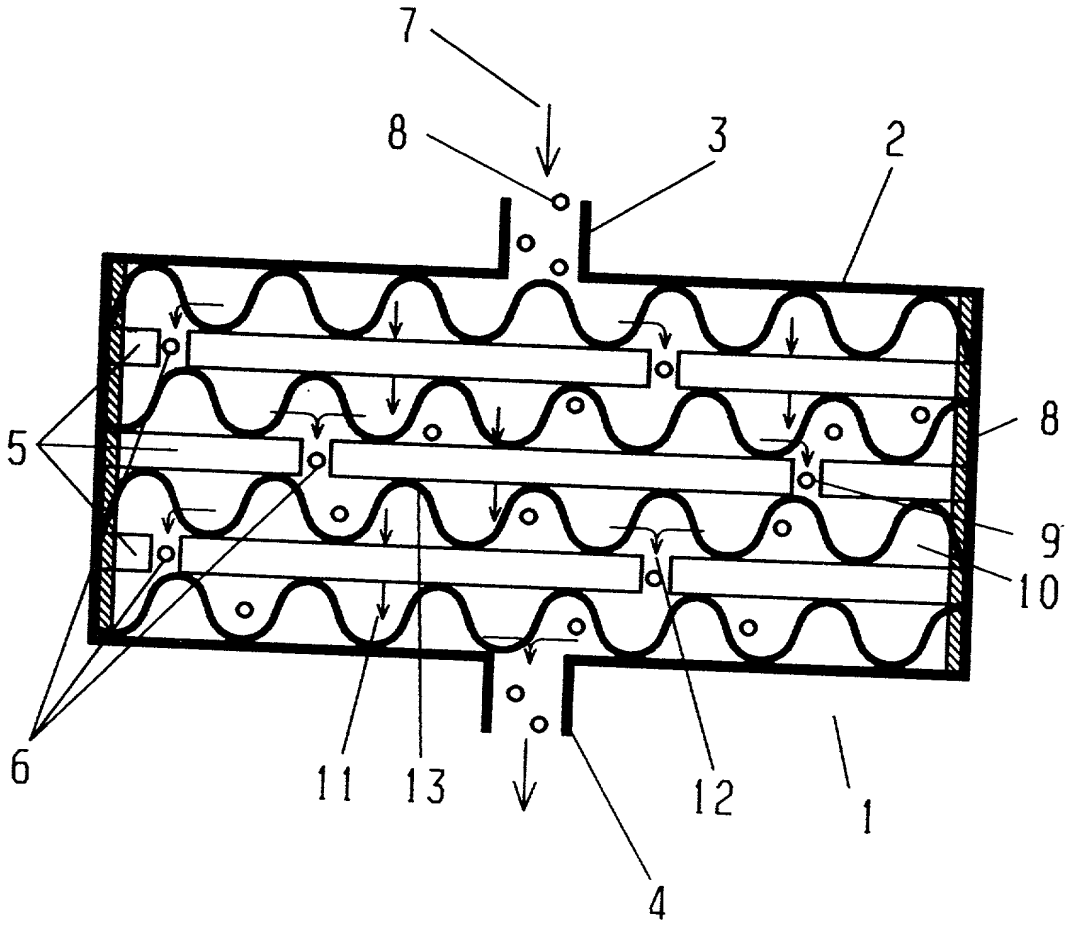

Fig. 1

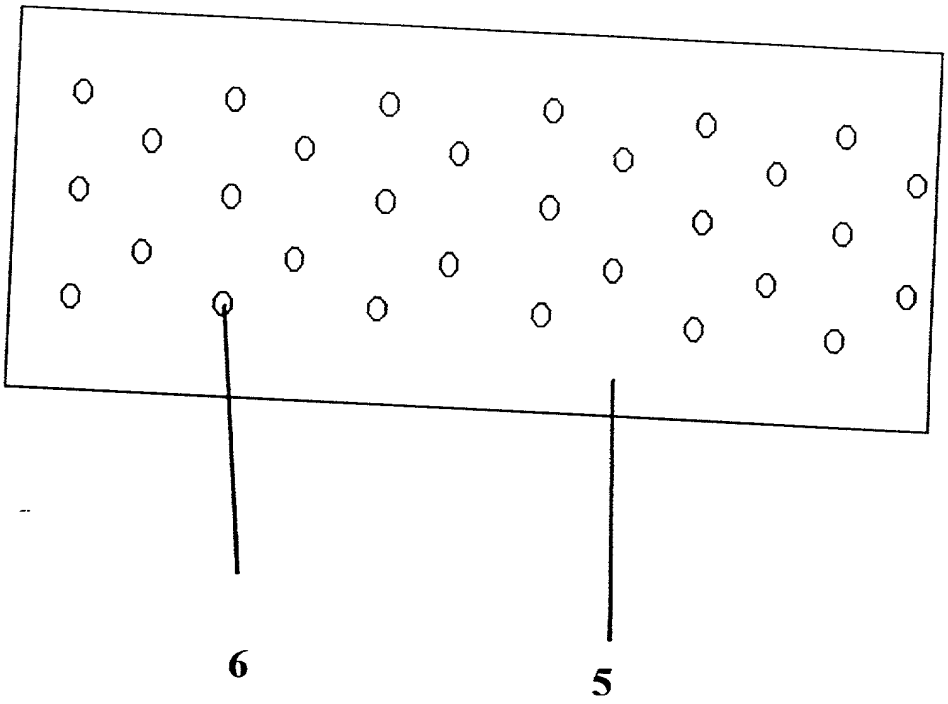

Fig. 2

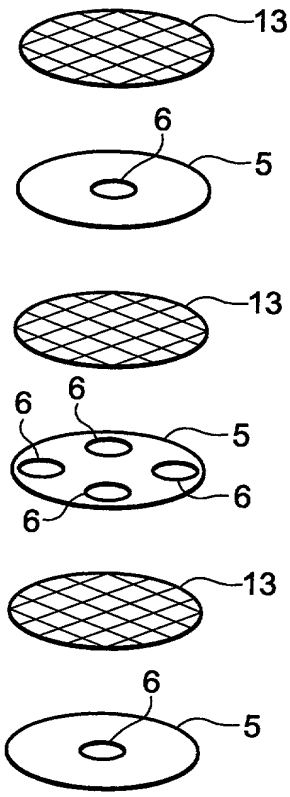

Fig. 3

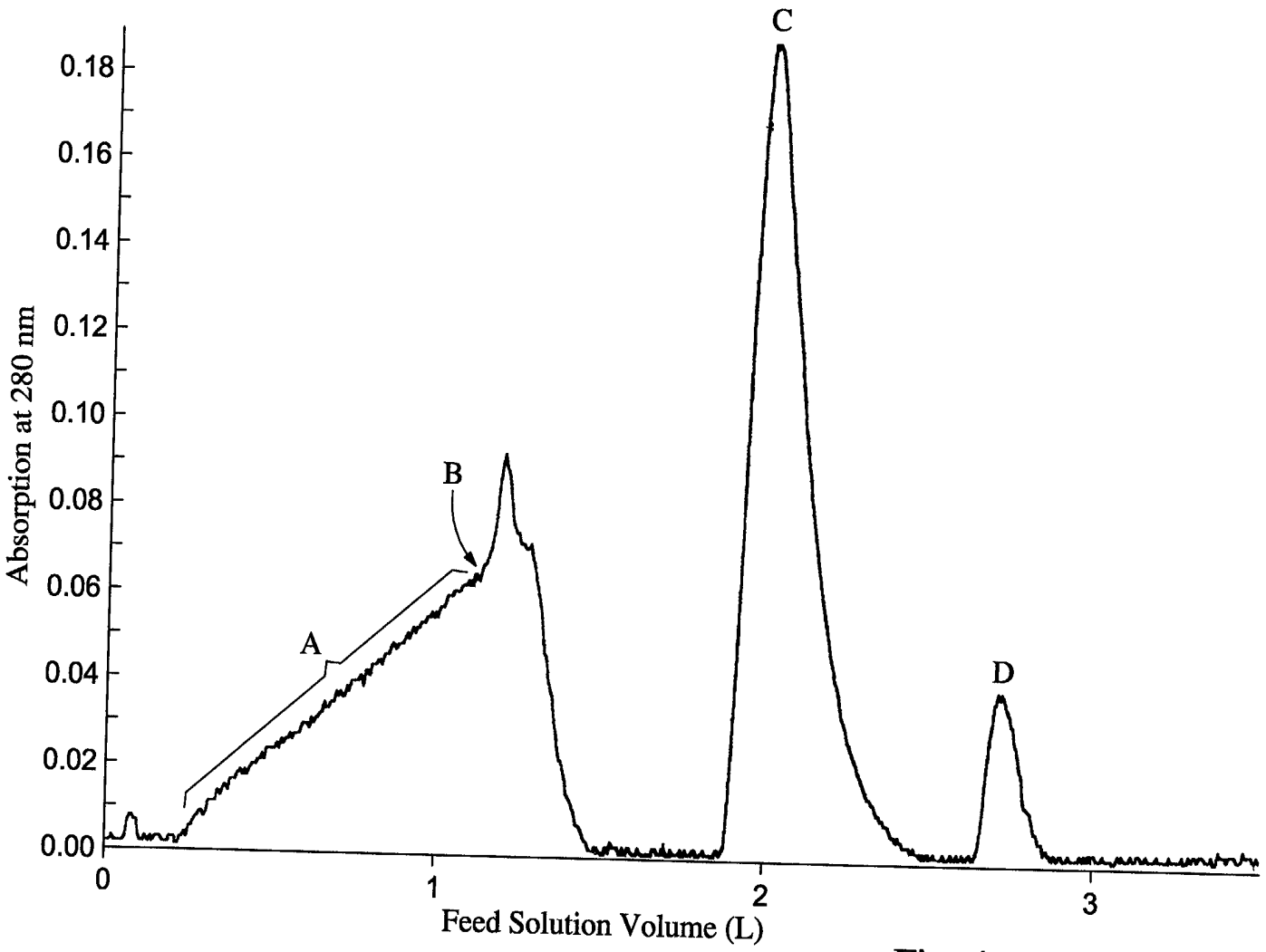

Fig. 4

DECLARATION

As below named inventors, we hereby declare that:

Our residences, post office addresses and citizenships are as stated below next to our names,

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ADSORPTIVE MEMBRANE DEVICE FOR TREATING PARTICLE-LADEN LIQUID FEEDS

the specification of which

[X] is attached hereto.

[ ] was filed on _____ as Application Serial No. _____ and was amended on _____. (if applicable)

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

We hereby claim foreign priority benefits under Title 35, United States Code, §365(b) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

			Priority Claimed
199 43 921.4 (Number)	GERMANY (Country)	14 SEPT 1999 (Day/Month/Year Filed)	[X] Yes [ ] No
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	[ ] Yes [ ] No
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	[ ] Yes [ ] No

We hereby claim the benefit under Title 35, United States Code, §120, of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

PCT/EP 00/08678	6 SEPT 2000	pending
(Application Ser. No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Ser. No.)	(Filing Date)	(Status) (patented, pending, abandoned)

We hereby declare that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION EXAMINING OPERATIONS

Applicants : Wolfgang Demmer and Dietmar Nussbaumer

Serial No. :

Filed : (concurrently herewith)

Title : **ADSORPTIVE MEMBRANE DEVICE FOR TREATING PARTICLE-LADEN LIQUID FEEDS**

POWER OF ATTORNEY

I, Dr. Eric Janssens, President, declare that I am the President of SARTORIUS AG, and am authorized to execute this document on its behalf. SARTORIUS AG is the assignee of the entire right, title and interest in the above-referenced patent application and hereby appoints Jacob E. Vilhauer, Jr., Reg. No. 24,885, Charles D. McClung, Reg. No. 26,568, Dennis E. Stenzel, Reg. No. 28,763, Donald B. Haslett, Reg. No. 28,855, William O. Geny, Reg. No. 27,444, J. Peter Staples, Reg. No. 30,690, Nancy J. Moriarty, Reg. No. P-40,733, Bruce W. DeKock, Reg. No. P-40,585, Kevin L. Russell, Reg. No. 38,292 and Timothy A. Long, Reg. No. 28,876, all members of the firm of CHERNOFF, VILHAUER, McCLUNG & STENZEL, 1600 ODS Tower, 601 S.W. Second Avenue, Portland, Oregon 97204-3157, telephone number (503) 227-5631, its attorneys, jointly and individually, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

SARTORIUS AG

Dated: 1/8, 2001

Dr. Eric Janssens, President